Synthesis of DL-α-Amino-β-(3-methyl-2-indole)propionic Acid

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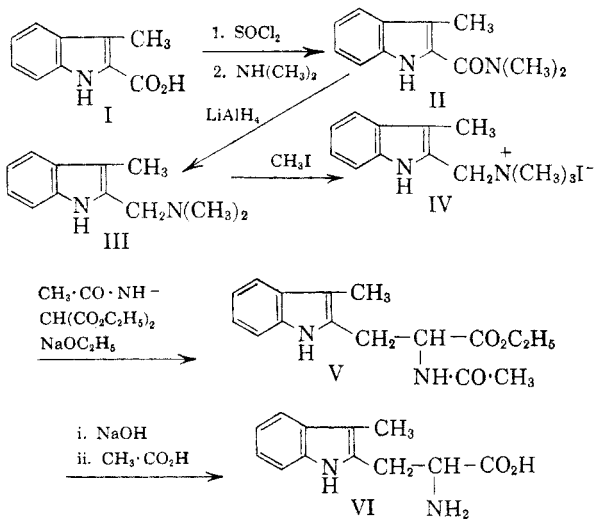
Of the six possible methyltryptophanes with the methyl substituent and the alanine side chain in the the various positions of the pyrrole portion of the indole nucleus, three have already been reported, *viz*, 1-methyltryptophane,[1] 2-methyltryptophane,[2] and 3-methyl-1-isotryptophane.[3] In view of the interest in the antimetabolite properties[4] of methyltryptophanes[5] and methylisotryptophanes[3,6] it was considered desirable to synthesize 3-methyl-2-isotryptophane, *i.e.*, α-amino-β-(3-methyl-2-indole) propionic acid (VI). The synthesis was patterned after the method first reported by Kornfeld[7] and later improved by Snyder and Cook[6] for the synthesis of 2-isotryptophane and was achieved as indicated in the accompanying chart.



By means of the acid chloride, 3-methyl indole-2-carboxylic acid (I) was converted into the dimethylcarboxamide (II) which was reduced in 57% yield by lithium aluminum hydride to 2-dimethylaminomethyl-3-methylindole (III). The methiodide IV, like the methiodides[6] of 2-isogramine and 6-methyl-2-isogramine, when reacted with the sodio derivative of ethyl acetamidomalonate in refluxing ethanol directly furnished the substituted propionic ester V in 91% yield. Saponification of V gave the amino acid VI in 58% yield.

The intermediate III was initially sought to be prepared by cyclization of 2-dimethylaminoacetamido-1-ethyl benzene by reaction with sodamide. The product was found to be an inseparable mixture of both the starting base and III and hence was unsuitable for further use.

EXPERIMENTAL

3-Methylindole-2-carboxylic acid dimethylamide (II). To a suspension of 3-methylindole-2-carboxylic acid[8] (11.3 g., 0.065 mole) in petroleum ether (150 ml.) contained in a flask provided with a calcium chloride drying tube was added thionyl chloride (25 g., 0.21 mole) and the mixture was allowed to stand for 20 hr. The dark colored mixture was freed of solvent and excess thionyl chloride *in vacuo*. The residue was taken up in toluene (150 ml.) and filtered from some insoluble material. To the clear toluene filtrate cooled in ice was added, in succession, a solution of pyridine (11.5 ml.) in toluene (15 ml.) and a toluene solution (35 ml., 20%) of dimethylamine (0.156 mole). The mixture was kept in an ice bath for 0.5 hr. and then at room temperature for 3 hr. The crystalline precipitate was collected and washed with water to give 6.6 g. of product, m.p. 172–174°. Concentration of the toluene filtrate after washing with water gave an additional 2.4 g. of material m.p. 172–174°; total yield 69%. A sample after two crystallizations from 95% ethanol had m.p. 174–176°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.2; H, 7.0. Found: C, 71.2; H, 7.1.

2-Dimethylaminomethyl-3-methylindole (3-methyl-2-isogramine) (III). Lithium aluminum hydride (8 g., 0.21 mole) was suspended in dry ether (400 ml.) in a flask fitted with a Soxhlet extractor. The amide II (13.2 g., 0.065 mole) was placed in the Soxhlet thimble and extracted continuously for a period of 40 hr. The reaction mixture was then worked up in the manner described[6] for the preparation of 1-methyl-2-dimethylaminomethyl indole and gave a colorless viscous product; 7 g. (57%), b.p. 148°/2 mm. The base which turned yellow on standing crystallized during the course of a month and was recrystallized from petroleum ether; m.p. 65.5–66°.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.6; H, 8.6. Found: C, 76.8; H, 8.3.

The above base furnished a picrate readily which after two crystallizations from ethanol had m.p. 210°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.8; H, 4.6. Found: C, 52.1; H, 4.8.

2-Dimethylaminomethyl-3-methylindole methiodide (3-methyl-2-isogramine methiodide) (IV). A solution of methyl iodide (4 g., 0.028 mole) in dry ether (10 ml.) was mixed with a solution of III (4 g., 0.021 mole) in dry ether (20 ml.). The methiodide crystallized immediately and was collected after 1 hr. at room temperature; yield 5 g. (72%). The product had no sharp melting point, decomposition occurred above 180° over a wide range. A sample for analysis was obtained by recrystallization from 95% ethanol.

Anal. Calcd. for $C_{13}H_{19}IN_2$: C, 47.3; H, 5.8. Found: C, 47.7; H, 5.8.

Ethyl-α-acetamido-β-(3-methyl-2-indole) propionate (V). To a solution of sodium (0.14 g., 0.006 g.-atom) in absolute ethanol (20 ml.) was added ethyl acetamidomalonate (1.4 g., 0.006 mole) and a solution of the methiodide IV (2 g., 0.006 mole) in absolute ethanol (70 ml.). The mixture was refluxed for 18 hr. with a stream of nitrogen passing through the reaction flask. Excess alcohol was removed *in vacuo* and the residue diluted with water (60 ml.). Pink colored crystals separated on gradual cooling and were collected and dried; m.p. 140–145°; yield 1.6 g. (92%). The analytical

(1) Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 3787 (1948).
(2) Rydon, *J. Chem. Soc.*, 705 (1948).
(3) Swaminathan and Ranganathan, *J. Org. Chem.*, **22**, 70 (1957).
(4) Martin, *Biological Antagonism*, The Blakiston Company Inc., New York, 1951, p. 131.
(5) See 3 for references to methyltryptophanes.
(6) Snyder and Cook, *J. Am. Chem. Soc.*, **78**, 969 (1956).
(7) Kornfeld, *J. Org. Chem.*, **16**, 806 (1951).
(8) Wislicenus and Arnold, *Ann.*, **216**, 336 (1888).

sample was obtained after two crystallizations from benzene and melted at 151–152°.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.6; H, 7.0. Found: C, 66.3; H, 6.8.

DL-*α-Amino-β-(3-methyl-2-indole) propionic acid* (DL-*3-methyl-2-isotryptophane*) (VI). Crude V (1.6 g., 0.006 mole) was mixed with a solution of sodium hydroxide (2.3 g., 0.057 mole) in water (23 ml.) and the mixture refluxed in a copper flask for 18 hr. Toward the end of this period, the reaction mixture was refluxed with Norit and filtered hot. The filtrate when acidified with glacial acetic acid gave an initial crop (125 mg.) of some infusible material. The filtrate from this initial crop was concentrated by evaporation to give successive crops totaling 0.7 g. (58%) of amino acid; m.p. 205–214°. A sample for analysis was prepared by evaporating a solution of the amino acid in hot water until enough material was obtained. This material was rinsed with a small amount of ethanol and the crystals dried *in vacuo* at 100° for 12 hr.; m.p. 219–223°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5. Found: C, 66.3; H, 6.8.

The aminoacid gave a positive Ninhydrin test. The R_f value found in butanol–acetic acid–water (4:1:5) was 0.69.

2-Chloracetamido-1-ethylbenzene. To a solution of *o*-aminoethylbenzene (39.1 g., 0.32 mole) in chloroform (80 ml.) was added pyridine (30 g., 0.43 mole) and chloracetyl chloride (38.4 g., 0.34 mole) with stirring and cooling. After addition was over, the reaction was completed by heating on a water bath for 0.5 hr. and the mixture poured into water (500 ml.). The chloroform layer was separated and the aqueous layer again extracted with chloroform. The combined extracts were washed with water, dried over calcium chloride, and chloroform removed. The residue was crystallized from methanol; m.p. 88–90°; yield 58 g. (91%).

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.7; H, 6.1. Found: C, 60.7; H, 6.3.

2-Dimethylaminoacetamido-1-ethylbenzene. A solution of 2-chloracetamido-1-ethylbenzene (33 g., 0.167 mole) in dry benzene (330 ml.) was mixed with a 4% solution (400 ml., 0.356 mole) of dimethylamine in benzene and the mixture was allowed to stand overnight. Dimethylamine hydrochloride which had separated was removed by washing with water and the base extracted from the benzene layer with 2*N* hydrochloric acid. The acid extract was made basic with ammonia and the oil which separated extracted with ether. The ether extract was stripped of solvent and the residue distilled; b.p. 174–176°/5 mm. (also 148–149°/1 mm.); yield 24.5 g. (71%). The product solidified on cooling and was crystallized from petroleum ether; m.p. 39°.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.8; H, 8.8. Found: C, 69.4; H, 8.7.

The base furnished a methiodide which was crystallized from a mixture of methanol and ether; m.p. 120–125°.

Anal. Calcd. for $C_{13}H_{21}IN_2O$: C, 44.8; H, 6.1. Found: C, 45.2; H, 6.1.

Attempts to prepare a crystalline picrate of the base failed.

Reaction of 2-dimethylaminoacetamido-1-ethylbenzene with sodamide. An ether solution (25 ml.) of 2-dimethyl aminoacetamido-1-ethylbenzene (15.2 g., 0.074 mole) was mixed with sodamide (8 g., 0.205 mole) in a 250-ml. 3-necked flask in an atmosphere of nitrogen and the ether was removed. The dry residue was heated on a metal bath to 310° over a period of 0.5 hr. and maintained at that temperature for an additional 0.25 hr. The reaction mixture was then cooled, decomposed cautiously with ethanol (25 ml.) followed by water (100 ml.) and extracted with benzene. The benzene solution was extracted with two 60-ml. portions of 7% hydrochloric acid. The acid extract was made alkaline with sodium carbonate and base taken up in benzene. The benzene layer after drying over solid potassium hydroxide furnished crude liquid (11.7 g.) which was fractionated *in vacuo* through a 6″ Vigreux column. After a forerun (1.5 g.) at 113–115°/1.5 mm., the main fraction (9 g.) was collected at 170–175°/1.5 mm. Refractionation of the latter afforded fractions I (1.4 g.) and II (7 g.) with b.p. 154–158°/1.5 mm. and 165–168°/1.5 mm., respectively. Each fraction afforded a picrate which after crystallization from ethanol or methanol had m.p. and mixed m.p. 206–208° with an authentic specimen of the picrate of 2-dimethylaminomethyl-3-methylindole. With methyliodide, both fractions gave a methiodide m.p. 110–115° which after crystallization from a mixture of methanol and ether had m.p. 120–125° undepressed by the methiodide of the uncyclized base. In other runs, whereas the different fractions gave consistently the same picrate, the methiodides obtained had varying melting points and were apparently mixtures of the methiodides of both the starting material and product.

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Syntheses of Pyrrolizidine, Indolizidine, and Related Compounds

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We[1] found that the treatment of diethyl 5-oxoazelate (Ia) with ammonia afforded a compound of Δ^5-piperidone type (IIa) and subsequent high-pressure hydrogenation of it with copper chromite catalyst proceeded successfully to quinolizidine (IIIa). An application of these reactions for preparing a diazatricyclo compound, 9-methyl-9-azahexahydrojulolidine (VIa), from 1-methyl-3,5-bis(β-ethoxycarbonylethyl)-4-piperidone (IVa) was also reported by us.[1] It is, therefore, of interest to study this reaction on other keto diesters.

When diethyl 4-oxopimelate (Ib),[2] diethyl 4-oxosuberate (Ic),[2] 1-methyl-3,5-bis(ethoxycarbonylmethyl)-4-piperidone (IVb), and 1-methyl-3-(β - ethoxycarbonylethyl) - 5 - (ethoxycarbonylmethyl)-4-piperidone (IVc) were treated with ammonia in alcohol or water, all were converted to monocyclic (IIb and IIc, in 40–50% yield), or bicyclic (Vb and Vc, in 20–30% yield) lactams respectively.

These lactams did not show any absorption bands in the ultraviolet region above 200 mμ (*cf.* the lactams,[1] IIa and Va showed their maxima at 203 mμ in water). In the infrared, the stretching vibrational bands for the ring carbonyl (-CONH-)[1] were observed at 1724, 1712, 1725, and 1704 $cm.^{-1}$ respectively for IIb, IIc, Vb, and Vc, while the bands of IIa and Va were located at 1675 and 1684

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(2) N. J. Leonard and W. E. Goode, *J. Am. Chem. Soc.*, 72, 5404 (1950).